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| 10/721,763 | 11/26/2003 | Eiji Mori | 081356-0207 | 6356 |

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| EXAMINER | |
|---|---|
| KAUFMAN, CLAIRE M | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/721,763 | MORI ET AL. | |
| | Examiner | Art Unit | |
| | CLAIRE KAUFMAN | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *63-104 and 108-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-104 and 108-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/08 has been entered.

### *Response to Amendment*

The declaration under 37 CFR 1.132 filed 3/26/08 is sufficient to overcome the rejections under 35 USC 102 of claims 63-104 and 108 based upon each of Griffith et al., US 7,244,429, and US 6,342,369.

The rejection of claims 63-104 under 35 USC 112, first paragraph, new matter, is withdrawn in view of the submission (1/22/08) of proof of filing on 11/28/03 and the request for change of filing date to 11/28/03.

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims, however, see the new objection to the claims below.

### *Specification*

The disclosure is objected to because of the following informalities: Tables 1-2 beginning on page 56 shows no information because all the symbols for cross-reactivity are identical. Tables 3-4 on pages 61-63 does not use the symbols of the legend and, therefore, provide no information. Appropriate correction is required.

### *Claim Objections*

Claims 64, 69, 74, 79, 84, 89,94, 100, 101 and 108-112 are objected to because of the following informalities: When the claims were amended, new words were added (underlining) without lining through the words intended to be deleted. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-104 and 108-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibody 0304 or 0322 or a functional fragment of either monoclonal antibody which is monomeric and free of any polymeric forms or (claims 103-104) a therapeutic agent against tumors comprising said monoclonal antibody or functional fragment thereof as an active agent or (claims 108-112) a method of producing said monoclonal antibody or functional fragment thereof comprising the step of immunizing a non-human animal with TRAIL-R2 or an extracellular (ECD) fragment thereof, does not reasonably provide enablement for other monoclonal antibodies or functional fragments thereof which are only present in monomeric form or for a prophylactic agent against tumors comprising said monoclonal antibody or fragment thereof or for a method of producing said monoclonal antibody or functional fragment thereof comprising the step of immunizing a human or immunizing an animal with a DNA containing the gene encoding all or part of the ECD of TRAIL-R2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 64-102 are drawn to a monoclonal antibody which is in monomeric form without polymeric forms and which binds TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 independent of other exogenous factors. Claims 103-104 are drawn to a "prophylactic or therapeutic agent against tumors" comprising the antibody or functional fragment thereof of claim 63 as an active ingredient. Claims 108-112 are drawn to a method of producing the antibody of claim 63.

The specification teaches three monoclonal antibodies which are able to induce apoptosis in carcimoma cells in the absence of cross-linking polyclonal antibody. The polymeric fractions of each of the three antibodies induced apoptosis in the absence of cross-linking by another antibody. However, the monomeric fraction of only monoclonal antibodies 0304 and 0322 induced apoptosis in the absence of cross-linking. The monomeric fraction of antibody H-48-2

did not induce apoptosis (Figures 17a-17f and pages 113-115). The specification only discloses these three antibodies as having been fractionated by HPLC.

While the prior art teaches antibodies that induce apoptosis in the absence of cross-linking by different antibody, the prior art does not teach fractionation of anti-TRAIL receptor antibodies. Additionally, in the declaration filed 3/26/08 (executed 4/2/08), it is shown that prior art antibody TRA-8 (US 7,244,429) when purified was able to induce apoptosis without cross-linking by a different antibody (Experiment 3 of the declaration): "The purified TRA-8 induced apoptosis in the absence of the cross-linking agent dependent on the concentration." However, when fractionated, the monomeric fraction of TRA-8 did not induce apoptosis (Experiment 5 of the declaration):"Therefore, it was revealed that the activity of inducing TRA-8 in the absence of the cross-linking agent depended on the polymer." Therefore, prior art antibody TRA-8 appears to have the properties of antibody H-48-2 of the instant application, which does not meet the limitations of the instant claims. The declaration on page 3, notes that prior art antibody M413 of Griffith et al. was not available to the public. In that section it is stated that, "Even without cross-linking, however, antibodies themselves generally form an aggregate spontaneously." In the declaration (p. 2), Dr. Motoki, presents evidence that almost all of the recombinant single chain 16E2 antibody of prior art US 6,342,369, was in polymeric form . It is concluded that "the apoptosis-inducing effects of the 16E2 antibody are due to its polymeric form; hence, that 16E2 does not function as "a single substance without polymer."" Dr. Motoki's final conclusion is as follows (paragraph 9 of the declaration): "In summary, I conclude that none of the prior-art antibodies can induce apoptosis in monomeric form. We found that the prior-art antibodies were able to induce apoptosis only when they formed polymeric antibody aggregates."

Therefore, the examples of the instant specification and the evidence and conclusion of the declaration support the unpredictability of making an antibody with the claimed limitations. This situation is unlike that of *Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed.Cir. 1986) in that here here is a need for more than "sophisticated, competent people [to] perform the screening and that the screening process is labor-intensive and time-consuming." This instant invention requires not only the isolation of particular monoclonal antibodies, *i.e.,* ones that bind to TRAIL-R2 and induce apoptosis in carcinoma cells, but also the identification of those monoclonals which possess apoptosis-inducing activity when monomers

in the absence of exogenous factors. This is an extremely limited scope compared to the antibodies at issue in the *Hybritech* case.

Further, the nature of the invention is such that only a portion of those monoclonal antibodies able to induce apoptosis upon binding to TRAIL-R2 in the absence of exogenous factors have monomeric fractions with that property as evidenced by the specification and declaration filed 3/26/08 (4/2/08). The prior art shows no fractionation of antibodies selective for TRAIL receptors and which induce apoptosis upon binding. The declaration by Dr. Motoki concludes that the activity of the prior art antibodies which bind TRAIL-R2 and induce apoptosis without cross-linking is due or most likely due to the polymeric form(s) of the antibodies instead of the monomeric form. Even though the relative skill of those in the art is high, fractionation of antibodies to separate monomeric and polymeric forms is not routine in the apoptosis or TRAIL receptor art. The art provides no predictability about the ability of a monomeric fraction of any give antibody to meet the limitations required in the claims. The specification provides working examples of only three monoclonal anti-TRAIL-R2 antibodies that induced apoptosis upon binding to TRAIL-R2, and of these, only two had monomeric fractions which retained the ability to induce apoptosis in the absence of cross-linking (or exogenous factors). The claims have breadth as currently written because they are drawn to a genus of antibodies. While the specification provides guidance by the inventors about assays that may be used to screen antibodies, the results are completely unpredictable--even at the point one has isolated a monoclonal antibody which can induce apoptosis upon binding to TRAIL-R2--because monomers of that antibody may or may not also induce apoptosis upon binding without exogenous factors. For these reasons and those discussed above, it would require undue experimentation to make and/or use the invention.

Even if the full scope of the claimed antibody was enabled, a prophylactic agent (claims 103-104) is not. It cannot be determined who or when one will get a TRAIL-R2-responsive tumor. Neither the prior art nor the specification provides information to allow the skilled artisan to anticipate the need for the antibody. Also, antibodies have limited half-lives and their activity in vivo is time-limited. Additionally, while immunization for the production of antibodies is well known in the art, immunization of humans for the purpose of antibody isolation is not, nor is the immunization of humans against TRAIL receptors. Indeed, such immunization could have

significant deleterious effects such as induction of apoptosis in noncancer cells. Therefore, while immunization of non-human animals for producing the antibody of claim 63 is enabled, immunization of humans is not. Lastly, immunization with DNA containing the gene encoding all or part of the ECD of TRAIL-R2 amounts to gene therapy, which is complex and difficult.. This method is extremely unpredictable and has no support in the prior art for wide application. There is no showing in the specification that the required translation of the TRAIL-R2 encoding DNA would be possible within a cell in an animal. The are no examples in the specification of production of the claimed antibody by immunization with DNA. There is insufficient guidance to allow the skilled artisan to practice the method by this manner with a reasonable expectation of success and without undue experimentation.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63, 64, 69, 74,79, 84,89, 94, 100, 101, 102 and 108 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 108 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the method of obtaining the monoclonal antibody which is only present in monomeric and not polymeric form and which induced apoptosis. This is an essential step because this is a critical feature of the antibody made, *i.e.*, the antibody of claim 63. While step (iv) is to separating a monomeric fraction which binds TRAIL-R2, this step is not linking to the next step (v), which is "evaluating the activity of inducing apoptosis of said monoclonal antibody". There is no limitation in (v) that the monoclonal being evaluated is only the monomeric fraction (*i.e.*, that is the "single substance").

Claims 63, 64, 69, 74,79, 84,89, 94, 100, 101, 102 and 108 are indefinite because they proscribe an active step to a passive product. That is, the antibody is a "single substance without **forming** a polymer". Also, if it does not form a polymer, it is necessarily a monomer. The

specification uses the term "monomer", which is much more clear than "single substance". The following language is suggested to clarify and reflect the teachings of the specification: "~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms and which binds to TRAIL-R2....."

Claims 63, 64, 69, 74,79, 84,89 and 94 are indefinite because in line 4, the use of the term "and" between antibody and the functional fragment thereof requires both. Substitution of the term "or" would obviate this rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.
/Claire Kaufman/

Patent Examiner, Art Unit 1646

April 28, 2008